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The Use of Androgen Deprivation Therapy in Combination With Radiation for Localized Prostate Cancer

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Context: The combined use of androgen deprivation therapy (ADT) and radiotherapy in the initial treatment of intermediate- and high-risk prostate cancer is well established.

Objectives: This study aims to review level 1 evidence and *post-hoc* analyses from prospective studies to determine the benefit of the addition of ADT to curative radiotherapy in prostate cancer and provide suggestions for future combinatorial trials in localized disease.

Evidence Acquisition: We used PubMed with the terms "radiation", "ADT", and "prostate" to identify randomized controlled trials that compared curative therapy alone to curative therapy with androgen deprivation therapy conducted from 1980 to the present extracted by the senior author. For critical questions for which randomized data were unavailable, we used studies selected by the senior author that relied on *post-hoc* analyses from prospective randomized trials in an attempt to provide substantive answers.

Evidence Synthesis: There is strong and unequivocal evidence that variable-length ADT in combination with curative dose radiotherapy improves biochemical recurrence-free survival, cause-specific survival (CSS), and overall survival in intermediate- and high-risk prostate cancer.

Evidence Summary: ADT should be a component of treatment for most men with unfavorable intermediate- and high-risk prostate cancer receiving curative dose radiotherapy

Keywords: neoadjuvant, ADT, androgen deprivation therapy, prostate cancer, radiation therapy

INTRODUCTION/METHODS: THE USE OF ANDROGEN DEPRIVATION THERAPY IN THE UP-FRONT MANAGEMENT OF NONMETASTATIC PROSTATE CANCER

Already well established in the metastatic setting, over the last 30 years, the use of androgen deprivation therapy (ADT) in the treatment of nonmetastatic prostate cancer has increased as a result of multiple, now-seminal phase 3 trials showing its efficacy in combination with radiotherapy. This review will critically examine level 1 evidence and *post-hoc* analyses from randomized trials

supporting the combined use of ADT and radiotherapy in localized prostate cancer with the goal of guiding its appropriate application. Trials published between 1980 and the present were identified by the senior author through a comprehensive PubMed search using "radiation," "ADT," and "prostate" as the search items.

DEFINITIVE RADIOTHERAPY AND ADT: THE BEGINNING

Inferior outcomes in patients with bulkier primary lesions treated with external beam radiotherapy (EBRT) and indications of benefit from simultaneous estrogen or orchiectomy in unplanned subgroup analyses of Radiation Therapy Oncology Group (RTOG) trial 75-06 led early RTOG investigators to conceive of and execute RTOG 86-10 and RTOG 85-31 (1). These were well-designed, appropriately powered phase 3 trials that were conducted in parallel and intended to test the twin hypotheses that neoadjuvant and concurrent ADT with radiotherapy may have a synergistic benefit on loco-regional control (RTOG 86-10) and that adjuvant ADT may help to eliminate micrometastatic disease (RTOG 85-31).

RTOG 85-31 enrolled patients with T1-2N1 (including para-aortic nodes) or T3N0-1 disease, randomizing them to definitive dose RT (44–46 Gy to the prostate and regional lymphatics followed by a 20–25-Gy boost to the prostate bed) or definitive dose RT with the indefinite adjuvant (beginning the final week of RT) administration of the LHRH agonist goserelin (2). RTOG 86-10 recruited subjects with T2b-T4N0-1 disease with primary lesions ≥25 cm (2) on digital rectal examination. The external radiotherapy component of the treatment was identical to 85–31; however, the ADT was limited to 4 months of goserelin beginning 2 months prior to EBRT and given concomitantly with flutamide (3). Both trials were predominantly node negative in their composition.

The publication of their initial results in the mid-1990s was among the earliest prospective, randomized demonstrations of the benefit of the combined treatment of higher-risk prostate cancer with RT and ADT. More recently, both reported their long-term results. RTOG 85-31 demonstrated a 10% absolute improvement in overall survival at 10 years favoring the adjuvant ADT arm (49% vs. 39%, $p = 0.002$). This benefit held up after controlling for nodal involvement, centrally reviewed Gleason score, age, and clinical stage (the no-longer-used A–B vs. C) (4). RTOG 86-10 reported remarkably similar, albeit statistically insignificant, results, with 10-year OS favoring the short-course ADT arm (43% vs. 34%, $p = 0.12$); however, differences in distant failure rates were clearly significantly better in the ADT arm (35% vs. 47%, $p = 0.006$). Multivariate analysis confirmed the benefit of ADT in reducing distant failure after controlling for age, KPS, centrally reviewed Gleason score, and stage (again, B2 vs. C) ($p = 0.01$). Importantly, the statistical analysis used for the 86-10 update was that of competing risks, which gives a stronger sense of the true impact of the intervention after accounting for deaths unrelated to disease (5).

Simultaneous to the RTOG's investigations, the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Cooperative Group launched its own phase 3 trial examining the concurrent and adjuvant administration of ADT with EBRT, hoping to improve on what it acknowledged were abysmal rates of local control in higher-risk prostate cancer treated with radiotherapy. Beginning in May 1987, the group randomized 415 patients with T1-2N0M0 WHO grade 3 prostate cancer or T3-T4N0 disease of any grade to EBRT alone (50 Gy to the pelvic nodes with a 20-Gy boost to the gland) or EBRT with the concurrent administration of goserelin beginning on day 1 of EBRT and continuing for 3 years; the steroidal antiandrogen cyproterone was given for the first month. The 1997 publication of EORTC 22863 showed dramatic improvements in overall survival: 79% in the combined arm versus 62% in the EBRT alone arm ($p = 0.001$). Among patients who survived for >5 years, the disease-free rate was 85% in the combined arm versus 48% in the radiotherapy-alone cohort ($p < 0.001$) (6). At 10 years, the absolute magnitude of the overall survival benefit continued to hold, with an OS of 58% in the combined arm and 38% in the EBRT alone arm. Locoregional failures were few in the combined arm (6%) compared to the monotherapy group (23%) (7). It is worthwhile to note that in all of the aforementioned contemporaneously enrolling trials, the 10-year overall survival rates were approximately the same in the radiotherapy alone groups (between 34% and 38%).

These first-generation combination trials set the standard and helped to pose the questions that were then asked and answered by the 2nd-generation investigations, largely conducted over the course of the 1990s and first reported in the early 2000s.

DEFINITIVE RADIOTHERAPY AND ADT: DURATION IN HIGH-RISK PATIENTS

A question of obvious importance begged by the earlier trials was the length of androgen suppression in the high- and very high-risk populations (T3a–T4 or Gleason 8–10 or PSA >20). Consequently, RTOG conceived of and began accrual to a trial designed to provide the first glimpse at a definitive answer.

The RTOG 92-02 randomized patients with T2c-T4N0-1 prostate cancer with initial PSAs of <150 ng/ml to either 4 months of concomitant flutamide and goserelin, beginning 2 months prior to radiotherapy (the experimental arm of 86-10), or the same 4-month neoadjuvant and concurrent regimen followed by monthly goserelin for an additional 24 months (an approximation of the adjuvant, experimental arm of 85-31). The radiotherapy regimen was essentially the same as that used in the earlier protocols, and although node-positive patients were allowed, only 3%–4% of enrolled patients were N1. In 2003, the initial trial results were reported: the OS at 5 years among the entire cohort was indistinguishable, approximately 80% in both arms. There were, however, significant differences in rates of distant failure (17.4% vs. 11.9%, $p = 0.03$) and cause-specific survival (94.6% vs. 91.2%, $p = 0.015$), favoring the longer-course ADT. An unplanned subgroup analysis, conducted without the

provision of an interaction term, did show a 5-year OS benefit for those patients with Gleason 8–10 disease treated with extended ADT (81.0% vs. 70.7%, $p = 0.04$) (8). Long-term follow-up confirmed the absence of an overall survival benefit in the cohort as a whole (OS at 10 years was approximately 50% in both arms) but reaffirmed the initial improvements seen in disease-free survival, disease-specific survival, distant metastasis, local progression, and biochemical failure. Again, in an unplanned subgroup analysis not driven by a significant test for interaction, there was an OS benefit at 10 years for the subgroup of patients with Gleason 8–10 disease favoring extended ADT (45% vs. 32%, $p = 0.0061$). The authors rightly conclude that, if the subgroup analysis is to be believed, the failure to demonstrate an OS benefit in the entire group may be secondary to the relatively small proportion of patients (23%) with Gleason 8–10 disease (9).

The EORTC followed with the introduction of a trial designed to address the same question of ADT duration. The evolution of the thinking of the EORTC had led them to start with a trial that involved the extended use of ADT (concurrent and adjuvant for 3 years). EORTC 22961 was designed to walk back EORTC 22863: recognizing the difficulty patients had in tolerating extended castration and the putative risk of metabolic syndrome associated with it, they wanted to determine whether 6 months of androgen suppression was noninferior to the previously trialed 3 years. Beginning in 1997, EORTC 22961 enrolled patients with T1c-2bN1-2 or T2c-T4N0-2 disease with baseline PSAs up to 40× the upper limit of normal to a randomized noninferiority comparison of 6 months of the LHRH agonist triptorelin, beginning on day 1 of EBRT, to triptorelin for 36 months. In N+ patients, EBRT consisted of treatment to an initial field that included the prostate, seminal vesicles, and external, internal, and lower common iliac lymph node basins; N0 patients received only prostate and seminal vesicle RT. The nodes, when treated, received 50 Gy; the prostate and seminal vesicles received 70 Gy in all circumstances. The authors would have regarded the short-course ADT as inferior if the upper limit of the 95% confidence interval for the hazard ratio for overall survival exceeded 1.31.

In their initial report at 5 years, the cumulative mortality was 15.2% in the long-term group and 19.0% in the short-term group; the test for noninferiority was not significant ($p = 0.65$), and the upper limit of the hazard ratio was 1.79; prostate cancer-specific mortality at 5 years was 4.7% in the short-term group and 3.2% in the long-term group ($p = 0.002$ by log-rank) (10). The authors thus rightly argued that short-course ADT was inferior to long-course ADT for patients with T2c or greater prostate cancer. Although only 20% of enrolled patients had Gleason 8–10 disease, 73% had T3 tumors, making this study, like RTOG 92-02 that came before it, one of few with predominantly NCCN high-risk patients. One could argue that in patients with smaller-volume Gleason 8–10 disease, the EORTC data do not provide particularly robust evidence for the extension of ADT beyond 6 months, but this presumption is open to the standard critiques of *post-hoc* conclusions.

Perhaps in an attempt to anticipate the questions that would arise from the initial report of EORTC 22961, the Canadian trial, PCS IV, randomized patients with node-negative, NCCN-defined high-risk (PSA >20 or T3–T4 disease or Gleason 8–10) prostate cancer to 18 versus 36 months of neoadjuvant, concurrent, and adjuvant ADT with radiation volumes and dosing similar to the earlier trials (44 Gy to the pelvic nodes with the prostate treated to 70 Gy). To our knowledge, PCS IV was the first trial of RT + ADT trial to use modern risk stratification, which was in part developed from information gleaned from preceding trials, as an eligibility requirement.

In the PCS IV, the Canadians showed a distinct trend towards improved 5-year OS in the long-course arm (91% vs. 86%, $p = 0.07$). However, there was not a difference in 10-year OS (62% vs. 62%, $p = 0.7$) (11). There were also neither significant improvements in disease-specific survival at 5 years (98% vs. 97% for long course vs. short course) nor in rates of biochemical, regional, or distant failures. Of note, while the study was promoted as a refutation of the need for 36 months of androgen suppression in high-risk patients, the trial was not designed as a noninferiority study. Although there was a borderline significant difference in OS favoring long course ADT at the 5-year follow-up mark, the absence of difference in overall survival at the 10-year time point suggests that there may not be a significant difference in terms of survival between these two regimens.

Finally, Zapatero et al. reported initial results for DART 01/05 (12). Using modern NCCN risk categories, the trial enrolled and stratified 355 intermediate and high risk (T3 or Gleason 8–10 or PSA >20–100) patients. Randomization was to either 4 months of ADT (with the first two neoadjuvant months consisting of combined blockade with an LHRH agonist and antiandrogen and the remainder of goserelin alone) or 28 months, mimicking the arms from RTOG 92-02. The comparative difference lay with the dose of radiation used, with the Madrid group requiring 76–82 Gy of 3DRT. Up until the publication of this trial, all combination RT/ADT duration trials used a low, what we would regard today as inferior, dose of radiation. A question that thus naturally arose was whether an extension of ADT beyond a short course would provide consistent benefits when modern, higher-dose radiation was used. In the DART Trial, a median of 78 Gy was ultimately delivered, with 85% of patients receiving prostate-only RT. The study was powered to detect a 15% absolute difference in biochemical failure.

After a median follow-up of 63 months, and although not powered to detect such a difference, there was a statistically significant improvement in overall survival at 5 years favoring the longer-course arm (95% vs. 86%, $p = 0.009$); there were five prostate cancer-related deaths in the short-course arm and none in the long-course arm. Not unsurprisingly, there was an even larger absolute improvement in 5-year distant-metastasis free survival, again favoring the longer-course therapy (94% vs. 83%, $p = 0.01$). This benefit was essentially limited to the high-risk patients, where the absolute improvement of 15% in overall survival was significant. For the intermediate-risk patients, there was no significant overall, distant-metastasis-free, or biochemical failure-free survival benefit with extended therapy.

A thoughtful critique of this trial noted that a large portion of the differential mortality rate between the two arms was attributable to

nonprostate cancer deaths; with their analysis conducted using Kaplan–Meier methods, it is still an open question whether, had the authors chosen to use the cumulative incidence method, the results would have been as dramatic; presumably not (13). However, this study does provide evidence that long-duration ADT in high-risk patients is beneficial even when using modern external beam radiotherapy dosing.

Further de-escalation of ADT with an even shorter duration was evaluated in the TROG 03.04 RADAR study, which compared the benefit of 18 versus 6 months of ADT among intermediate- and high-risk patients (14). Included patients had locally advanced prostate cancer (defined as either T2b-4 N0 M0 or T2a N0 M0 with Gleason 7 or higher disease and PSA at least 10 μg/L) and were randomly allocated in a 1:1:1:1 fashion using a 2 × 2 factorial design to receive either short- or intermediate-term androgen suppression with definitive radiation treatment, both with or without zoledronic acid concurrent with ADT. Patients receiving short-term ADT were given 6 months of neoadjuvant leuprolide, and those receiving intermediate-term androgen suppression received an additional 12 months of adjuvant leuprolide.

From 2003 to 2007, 1,071 patients were enrolled, and at the time of reporting the results of the study, the median follow-up was 10.4 years without apparent interactions observed between groups based upon treatment with or without zoledronic acid. Prostate cancer-specific mortality was 9.7% for intermediate-term versus 13.3% for short-term ADT (hazard ratio (HR), 0.7; 95% confidence interval (CI), 0.50–0.98; *p*-value (*p*), 0.035). The results of this study suggested that while the use of zoledronic acid did not impact survival, intermediate-term was superior to short-term ADT for patients with intermediate- to high-risk disease.

Taking them together, the "duration trials" demonstrate significant improvements in overall survival with extended ADT for patients with the higher-risk disease (~18 months), regardless of whether they received a low-dose (70 Gy) or moderately dose-escalated (contemporary) external beam radiation (>76 Gy). However, the bulk of the survival benefit seems to come from the first 4 to 6 months of ADT administration; the absolute benefit derived from the extension of therapy is comparatively small (3.8% at 5 years in EORTC 22961 and 2.6% in RTOG 92-02).

This comparatively small absolute OS improvement with extended ADT naturally begs the question of whether we can further predict high-risk patients who would benefit from long-course ADT, or further intensification, versus high-risk patients whose outcomes would be satisfactory with shorter durations of therapy. After all, the extension of ADT can carry with it increases in competing, specifically cardiovascular, mortality, especially in older patients with multiple, pre-existing comorbidities (15).

D'Amico et al. published a reanalysis of the DFCI and TROG short-course ADT trials in an attempt to identify patients most likely to benefit from extended androgen suppression. Using the Prentice criteria, the authors identified both 1st posttreatment PSA and posttreatment PSA nadir as early surrogate endpoints for prostate cancer–specific mortality (PCSM) that explained a significant proportion of the benefit of treatment with ADT. In this combined analysis, patients with either a 1st PSA posttreatment of <0.5 ng/ml or posttreatment nadir PSA of <0.5 ng/ml—regardless of whether they received RT alone or RT+ADT—had exceptionally low PCSM; the PSA cutpoint value was chosen based on pre-existing evidence of its prognostic significance (16). Although only a hypothesis, the authors argued that for the patients who achieve either a 1st posttreatment PSA of <0.5 or a posttreatment nadir PSA of <0.5 after combined RT+ short-course ADT, lengthening the course of androgen suppression may provide no additional PCSM benefit (17). Furthermore, Zelefsky et al. have shown that, after controlling for total ADT duration and risk group, pre-RT PSA nadirs of <0.3 ng/ml after 3 months of neoadjuvant ADT are similarly predictive of distant failure and cause-specific survival (18).

In addition to PSA response as a determinant of ADT duration, there is also now robust data showing that genomic classifiers can accurately prognosticate distant metastatic risk within the subgroup of high-risk patients. Nguyen showed that for patients whose tumors had lower DECIPHER scores, the risk of distant metastasis was significantly lower compared to those with higher DECIPHER scores (19). NRG GU009 (NCT04513717) is now testing whether high-risk patients with lower DECIPHER scores can have their ADT duration shortened while simultaneously evaluating treatment intensification by adding apalutamide for those with higher DECIPHER scores.

In addition to PSA response and genomic classification, the STAMPEDE group, using a bespoke definition of very high-risk, node-negative prostate cancer (two of the following: MR evidence of T3/T4 disease, Gleason score 8–10, or PSA of ≥40) showed, with the addition of 24 months of abiraterone to 74 Gy in 37 fractions of prostate-direct radiation and ADT, dramatic improvements in both MFS (HR 0.60) and OS (0.70) (20).

Outside of refinement in predictive capacity in the high-risk cohort, further evolution in radiation techniques, whether it be extreme dose escalation (brachytherapy combination or SBRT) or treatment of pelvic nodes, may yet result in reductions in ADT duration or intensity. Tantalizing possibilities are suggested by the publication of ASCENDE-RT (21, 22). In a randomized comparison of dose-escalated EBRT to 78 Gy versus 32 Gy of EBRT followed by a 115-Gy low-dose rate brachytherapy boost, the majority of patients were high risk and all were treated with 12 months of androgen deprivation. At 5 years, the biochemical recurrence-free survival (bRFS) in the brachytherapy boost arm compared favorably to the bRFS of the long-course ADT arm in DART 01/05, suggesting that, at least for this endpoint, extreme dose escalation with 12 months of ADT may be noninferior to dose-escalated EBRT alone with 28 months of ADT. In addition, the recently published POP-RT trial showed a DMFS benefit with the addition of elective pelvic lymph node treatment in high-risk patients. Notably, in the STAMPEDE trial, pelvic nodes were omitted from the radiation fields. Would abiraterone still provide benefit in this very high-risk cohort had pelvic nodal irradiation been included?

Finally, the question of whether a shorter course, but more intensified, ADT could eliminate the need for longer duration and more toxic therapy is also of interest. The AASUR trial evaluated 6 months of ADT, abiraterone, and apalutamide combined with prostate-only directed SBRT in patients with very high-risk localized prostate cancer and reported at ASCO 2021 promising interim results suggesting an acceptably low risk of biochemical failure in this cohort (23).

DEFINITIVE RADIOTHERAPY AND ADT: BENEFIT IN INTERMEDIATE-RISK PATIENTS

While we have reviewed the question of the duration of ADT in high-risk patients, an open question that was again addressed by seminal trials conducted during the 1990s and first reported in the early 2000s was whether patients with intermediate-risk disease would benefit from short-course androgen suppression, or whether EBRT alone was entirely sufficient to the task of disease eradication.

The Dana-Farber group was the first to publish on this topic, with both initial and follow-up analyses (24, 25). D'Amico et al. randomized 206 patients, all of whom had T1–T2 disease and the vast majority of whom had Gleason scores of ≤7 (85%), to 6 months of combined androgen blockade (LHRH agonist and flutamide) with a radiation (67 Gy to the prostate and seminal vesicles) versus EBRT alone. Randomization occurred after stratification by groups based on PSA and Gleason scores. The reported results were dramatic: at 8 years, overall survival favored the short-term ADT + EBRT group, 74% versus 61% (p = 0.01). The benefit was almost entirely explained by the differential effects of the treatment on PCSM: 14 deaths in the combined arm versus 4 in the EBRT alone group (p = 0.007). An unplanned subgroup analysis based on Adult Comorbidity Evaluation 27 (ACE-27) surveys showed a significant interaction with treatment; the overall survival benefit with the addition of short-course ADT appeared limited to those patients with minimal or no comorbidities.

Contemporaneously recruiting (1994–2001), but later to report, RTOG 94-08 published their 10-year trial results wherein a largely low- (36%) and intermediate-risk (53%) cohorts were randomized to receive either short-course combined androgen blockade (flutamide and an LHRH agonist beginning 2 months prior to RT and continuing for a total of 4 months) and EBRT to the pelvis and prostate (66.6 Gy) or EBRT alone. With a median follow-up for surviving patients of 9 years, there was a significant improvement in 10-year overall survival favoring the ADT arm, 62% versus 57% (p = 0.03); this was largely explained by the difference in disease-specific mortality between the two arms: 8% versus 4% (p = 0.001). However, the benefit in overall and disease-specific mortality was limited to the patients with intermediate-risk disease; for these patients, a 10-year overall survival in the ADT arm was 61% versus 54% in the EBRT alone group; PCSM at 10 years was higher in the EBRT alone arm: 10% versus 3%—essentially the magnitude of the OS benefit, and similar to the PCSM benefit seen in the DFCI trial.

A question of critical import that the two aforementioned trials were not designed to answer was whether the impressive benefit obtained with the addition of short-course ADT to EBRT in intermediate-risk patients would hold in the modern era of dose escalation. A preliminary answer was provided by the published abstract of the third-generation PCS III trial: between 2000 and 2010, 600 patients with NCCN-defined intermediate-risk prostate cancer were randomized to 1 of 3 arms: 70 Gy with a short course of combined androgen blockade for 6 months beginning 4 months prior to RT (Arm 1), 76 Gy with the same ADT (Arm 2), or 76 Gy alone (Arm 3). With a median follow-up of 75.6 months, the authors reported both 5- and 10-year rates of disease-free and overall survival. Given the follow-up, the 5-year rates are more robust and it is on these that we focus: while there was no difference in OS at 5 years, there were significant comparative differences in disease-free survival (DFS) when comparing Arms 1 and 2 (the ADT arms) to Arm 3 (dose-escalated EBRT alone). The 5-year rates of DFS were 93% (Arm 1), 97.5% (Arm 2), and 86% (Arm 3). No firm conclusions should be drawn from an abstract alone, but these initial results suggest that dose escalation does not eliminate the need for short course ADT in intermediate-risk patients, and least in terms of preventing disease recurrence. The benefit of short-course ADT was further reinforced by the recent reporting of the long-term outcomes from the large intermediate-risk cohort that was enrolled in EORTC 22991. With a median follow-up of 12.2 years, there was a reduction in event-free survival (EFS) (HR = 0.53, $p < 0.01$) and a numerically and nearly statistically significant reduction in distant metastases (HR = 0.74, p = 0.065) and improvement in OS (HR = 0.74, p = 0.08); tests for interactions comparing patients treated with 74 and 78 Gy were not significant (26).

However, while PCS III and EORTC 22991 have provided strong support for the continued utility of short-course androgen suppression in the modern, high-dose RT era for intermediate-risk patients, the relatively recent bifurcation of the intermediate-risk group into favorable and unfavorable categories has led to the natural question of the relative benefit of short-course ADT within these two subgroups.

MSKCC investigators established the definition for this now NCCN accepted division in a robust retrospective analysis of over 1,000 NCCN-intermediate-risk patients treated with dose-escalated (≥81 Gy) EBRT (27). Patients received a median of 6 months of ADT at the discretion of the treating physician. In their initial multivariable screen, the authors found that ADT, Gleason 4 + 3 disease, percentage of positive cores with cancer >50%, and ≥2 intermediate-risk factors each predicted distant metastasis and PSA-recurrence-free survival. They then classified patients with any one of the aforementioned factors (Gleason grade 4 + 3, positive cores >50%, and 2 or more intermediate risk factors) as having unfavorable intermediate risk. After controlling for ADT use, they found that patients with unfavorable intermediate-risk disease had increased risks of

biochemical failure, local failure, distant failure, and, most importantly, prostate cancer-specific mortality. When analyzing the favorable intermediate-risk group, short-course ADT still improved PSA recurrence-free survival (93.6% vs. 80.9%), but it had no impact on distant failure or disease-specific mortality, although there were extraordinarily low-event numbers for these endpoints in this subgroup. For the unfavorable intermediate-risk group, ADT improved not only biochemical failure-free survival but decreased distant failures and prostate cancer-specific mortality. Keane et al. independently validated this subclassification of intermediate-risk patients, demonstrating no benefit for ADT in a favorable intermediate-risk cohort treated with brachytherapy (28). Contemporaneous with the MSKCC group, Castle et al. used a slightly different definition of unfavorable (Gleason 4 + 3 or T2c) and favorable intermediate risk to demonstrate a selective advantage for the addition of ADT to RT in the unfavorable group only; for this group, freedom from failure at 5 years was 74% for RT alone compared to 94% with the addition of short-course ADT (p = 0.01) (29). Finally, and most importantly, in their secondary analysis of RTOG 94-08, Zumsteg et al. showed that while unfavorable intermediate-risk patients benefited from the addition of short-course ADT added to radiation, those with the favorable intermediate-risk disease did not (30).

The recent abstract report of RTOG 08-15 has also shed further light on the role of ADT in intermediate-risk diseases. RTOG 08-15 (31) is a trial of intermediate-risk patients treated with dose-escalated radiotherapy (either EBRT only to a total dose of 79.2 Gy or in combination with either LDR or HDR brachytherapy) randomized to either RT alone or RT with 6 months of ADT. The trial included patients who had one or two (but not three) intermediate-risk factors, including clinical stage T2b–T2c, Gleason score 7, or PSA value of 10–20 ng/ml. Approximately 67% of patients had 1 intermediate-risk factor, and 12% were treated with a brachytherapy boost. After a median follow-up of 6.2 years, there was not a significant difference in 5-year overall survival associated with the addition of ADT to dose-escalated EBRT for patients with the intermediate-risk disease (HR, 0.85; 95% CI, 0.65–1.11; p = 0.22). However, the use of ADT in this population was associated with lower rates of PSA failure (HR, 0.52; 95% CI, 0.39–0.70; $p < 0.001$), distant metastases (HR, 0.25; 95% CI, 0.11–0.57; $p < 0.001$), and prostate cancer-specific death (HR, 0.10; 95% CI, 0.01–0.80; p = 0.007). Most importantly, in subgroup analyses of patients with 2–3 intermediate risk factors (a population enriched for patients with unfavorable intermediate-risk disease), the benefit of short-course ADT in reducing both biochemical failure and distant metastases persisted.

How do we integrate all of the above data into a coherent treatment recommendation for intermediate-risk patients receiving radiation? For favorable intermediate-risk disease, a single radiation modality, be it dose-escalated EBRT (including SBRT) or LDR brachytherapy monotherapy, may be sufficient to achieve high rates of cure for most patients. For the unfavorable intermediate-risk cohort, the addition of short-course ADT to either brachytherapy-based or dose-escalated EBRT regimens is the standard of care. Ongoing studies are evaluating whether extreme dose escalation in the form of SBRT or a combination of EBRT and brachytherapy may provide adequate dose escalation to obviate the need for ADT in the treatment of patients with unfavorable intermediate-risk diseases.

DEFINITIVE RADIOTHERAPY AND ADT: FUTURE DIRECTIONS

The recent publication of the MARCAP patient-level meta-analysis reaffirms the current standards of care for combining ADT with radiotherapy in both high- and intermediate-risk patients (32). This impressive effort will likely also shed additional light on the value of ADT in the favorable intermediate-risk cohort.

Multiple critical ongoing trials of systemic escalation and de-escalation trials using novel androgen receptor signaling inhibitors are either actively accruing or currently in follow-up, including NRG GU009 (NCT04513717) and GU010 (NCT05050084) using apalutamide, DASL-HiCaP (NCT04136353) using darolutamide, EnzaRad (NCT02446444) using enzalutamide, and AASUR (NCT02772588) using apalutamide and abiraterone. Even more novel is the INTREPId trial (NCT04025372) evaluating whether substitution of traditional ADT with darolutamide might provide quality-of-life benefits for patients with intermediate-risk disease.

This rich landscape of combinatorial trials will, as they report, undoubtedly improve outcomes for men with prostate cancer.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fruro.2022.890814/full#supplementary-material

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